

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Kai ROSSEN, et al.

GAU:

SERIAL NO:

EXAMINER:

FILED:

FOR: METHOD OF PRODUCING 5-FORMYL-2-FURYLBORONIC ACID

REQUEST FOR PRIORITY

COMMISSIONER FOR PATENTS
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SIR:

- ☐ Full benefit of the filing date of U.S. Application Serial Number , filed , is claimed pursuant to the provisions of **35 U.S.C. §120**.
- ☐ Full benefit of the filing date(s) of U.S. Provisional Application(s) is claimed pursuant to the provisions of **35 U.S.C. §119(e)**:
Application No. Date Filed
- ☒ Applicants claim any right to priority from any earlier filed applications to which they may be entitled pursuant to the provisions of **35 U.S.C. §119**, as noted below.

In the matter of the above-identified application for patent, notice is hereby given that the applicants claim as priority:

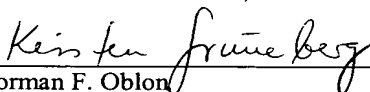
<u>COUNTRY</u>	<u>APPLICATION NUMBER</u>	<u>MONTH/DAY/YEAR</u>
EPC	02 021 439.1	September 25, 2002

Certified copies of the corresponding Convention Application(s)

- ☒ are submitted herewith
- ☐ will be submitted prior to payment of the Final Fee
- ☐ were filed in prior application Serial No. filed
- ☐ were submitted to the International Bureau in PCT Application Number
Receipt of the certified copies by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.
- ☐ (A) Application Serial No.(s) were filed in prior application Serial No. filed ; and
- ☐ (B) Application Serial No.(s)
☐ are submitted herewith
☐ will be submitted prior to payment of the Final Fee

Respectfully Submitted,

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The attached documents
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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk



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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Method of producing 5-formyl-2-furylboronic acid

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)
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METHOD OF PRODUCING 5-FORMYL-2-FURYLBORONIC ACID

The present invention refers to an improved method of producing 5-formyl-2-furylboronic acid.

5 The Suzuki coupling reaction is a well known method for the formation of aryl-aryl bonds, whereby an aryl borate is reacted with an aryl halide in a palladium catalyzed coupling reaction. The Suzuki coupling reaction is very useful in the synthesis of drugs and consequently it is under current investigation to provide suitable starting
10 materials.

One very useful building block is 5-formyl-2-furylboronic acid. Florentin et al. (Bull. Soc. Chim. Fr. 1976, 11-12, 1999) discloses the preparation of 5-formyl-2-furylboronic acid starting from 2-furaldehyde. The formyl functionality
15 of the 2-furaldehyde is protected as diethylacetal and said diethylacetal is metalated with methylolithium. The obtained lithiated furan is subsequently reacted with tributyl borate and after acidic quench the 5-formyl-2-furylboronic acid was isolated. Florentin et al. investigated the ¹H and ¹³C
20 NMR spectra of said furylboronic acid. There is no further disclosure regarding the reaction conditions, yield or purity of the obtained 5-formyl-2-furylboronic acid.

In an earlier paper Florentin et al. (C.R.Acad.Sc.Paris, Ser. C 1970, 270, 1608) describes the preparation of 5-
25 formyl-2-furylboronic acid by metalation of 2-formyl-5-bromofuran with butyllithium and subsequent reaction of the metalated furan derivative with n-butylborate. After acidic work-up the 5-formyl-2-furylboronic acid was obtained as white crystals in a 15% yield.

30 WO96/16046 describes the synthesis of 5-formyl-2-furylboronic acid whereby furfuraldiethylacetal is metalated with butyllithium in ether as a solvent at a temperature of -40°C. The reaction mixture is stirred at room temperature for additional 2 hours and subsequently

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again chilled to -40°C . A solution of trimethylborate in ether is added and subsequently heated to room temperature and then held at reflux. After acidic work-up and recrystallization 5-formyl-2-furylboronic acid was isolated
5 as a colorless solid in 26% yield.

McClure (Synthesis 2001, No.11, 1681-1685) describes a practical one-pot synthesis of 5-aryl-2-furaldehyde via palladium mediated Suzuki coupling of arylhalides with in situ generated 5-(diethoxymethyl)-2-furylboronic acid. 5-
10 (Diethoxymethyl)-2-furylboronic acid is used as building block because 5-formyl-2-furylboronic acid is considered to be cost-prohibitive and the described preparation methods of same suffer from low temperature requirements, capricious reproducibility, tedious work-up as well as
15 unsuitably low purity and isolated yields. McClure was not able to improve the isolation of 5-(diethoxymethyl)-2-furylboronic acid as well as 5-formyl-2-furylboronic acid and therefore decided to use a crude solution of 5-(diethoxymethyl)-2-furylboronic acid in the subsequent
20 Suzuki coupling.

Roschangar et al. (Tetrahedron 58 (2002) 1657-1666) describes the preparation of 5-formyl-2-furylboronic acid, whereby starting from furfural said boronic acid is obtained via metalation and subsequent addition of
25 triisopropylborate to the metalated furan derivative. Because of the difficulties described in the prior art like low temperature requirements, capricious reproducibility, tedious workup as well as unsuitably low purity and isolated yields Roschangar et al. did not try to isolate 5-
30 formyl-2-furylboronic acid. Therefore, they applied the boronic acid to a subsequent Suzuki coupling without further purification. 5-Formyl-2-furylboronic acid was obtained as crude reaction solution, only.

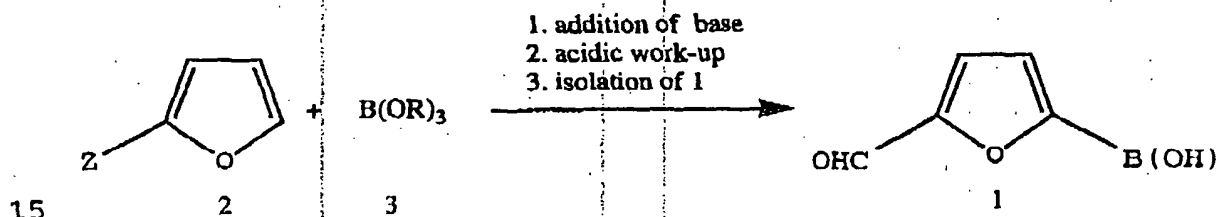
The object of the present invention is to provide a method
35 of producing 5-formyl-2-furylboronic acid with improved yield, stability and purity of the obtained 5-formyl-2-

furylboronic acid. A further object of the present invention is to improve and optimize the reaction conditions for preparing said boronic acid.

The technical problem of the present invention is solved by a method of producing 5-formyl-2-furylboronic acid comprising the steps of:

- a) addition of a base to a composition comprising a boric acid ester and 2-furaldehyde whereby the formyl functionality of the 2-furaldehyde is protected with a protective group, and
- b) acidic work-up of the reaction mixture of step a), and
- c) isolation of 5-formyl-2-furylboronic acid.

The following reaction scheme exhibits the method of producing of 5-formyl-2-furylboronic acid (1).



A base is added to a mixture comprising a protected 2-furaldehyde (2) whereby Z is the formyl functionality of the 2-furaldehyde which is protected with a suitable protective group and a boric acid ester (3) whereby R is a suitable residue. After completion of the reaction the reaction mixture is subjected to an acidic work-up and 5-formyl-2-furylboronic acid (1) is isolated.

In a preferred embodiment the boric acid ester of step a) is an alkylboric acid ester and/or arylboric acid ester. The alkylboric acid ester of step a) is preferable selected from the group consisting of B(OiPr)₃, B(OEt)₃, B(OMe)₃, B(OPr)₃, B(Obu)₃, and mixtures thereof.

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- The protective group with which the formyl functionality of the 2-furaldehyde is protected may be any protective group that is known to a person skilled in the art to be suitable. In a preferred embodiment the protective group is an O,O-acetal protective group or an N,O-acetal protective group. In case that the acetal protective group is an O,O-acetal protective group preferably the alcohol is selected from the group consisting of alkanols having 1 to 10 carbon atoms, alkandiolis having 1 to 20 carbon atoms, and mixtures thereof. In a preferred embodiment the protective group is selected from methanol, ethanol, propanol, butanol, ethylene glycol, 1,3-propane diol, and N-substituted ethanol amines.
- 15 In a preferred embodiment the base of step a) is selected from the group consisting of alkyl metal, metal amides, and mixtures thereof. Preferably the alkyl metal is alkyllithium, alkylsodium or alkylpotassium. In a further preferred embodiment the base of step a) is selected from
- 20 the group consisting of lithium hexamethyldisilazane, sodium hexamethyldisilazane, potassium hexamethyldisilazane, lithium diisopropylamide, butyl lithium, methyl lithium, ethyl lithium, propyl lithium, and mixtures thereof.
- 25 It is preferred that a solvent is present in step a). The solvent can be every solvent that is customary to a person skilled in the art, such as a solvent selected from the group consisting of tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, and mixtures thereof.
- 30 The addition of a base to a composition comprising a boric ester and the protected 2-furaldehyde may be carried out at a temperature of from -100°C to 30°C, preferably -78°C to 5°C, even more preferred from -30°C to 0°C, and most preferred from -20°C to 0°C, and -10°C to 0°C.

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The ratio of the base to the protected 2-furaldehyde in step a) is preferably of from 1,0 to 1,6 equivalents of base, preferably of from 1,0 to 1,4 equivalents, even more preferred of from 1,1 to 1,3 equivalents of base per mole protected 2-furaldehyde.

The ratio of the boric acid ester to the protected 2-furaldehyde is of from 1,0 to 1,8, even more preferred of from 1,2 to 1,5 moles, and most preferred of from 1,3 to 1,5 moles of boric acid ester per mole protected 2-furaldehyde.

In a preferred embodiment the acidic work-up in step b) is conducted by using an aqueous acid. The aqueous acid can be any acid that is customary to a person skilled in the art. Preferably, the aqueous acid is selected from the group consisting of hydrochloric acid, sulfuric acid, citric acid, acetic acid, formic acid, and mixtures thereof.

The acidic work-up of the reaction mixture of step a) can either be carried out by addition of an acid to the reaction mixture of step a), or by addition of the reaction mixture of step a) to an acid.

The acidic work-up of step b) can be carried out by temperature of from -10°C to 70°C , preferably from 0°C to 60°C , most preferred from 10°C to 50°C .

The isolation of 5-formyl-2-furylboronic acid of step c) can preferably be performed by means of filtration, centrifugation, and/or crystallization.

In a preferred embodiment the obtained 5-formyl-furan-boronic acid of step c) is further purified by means of recrystallization. The recrystallization can be performed by using any suitable solvent. It is preferred that the solvent is a polar solvent, such as acetonitrile, water, and mixtures thereof.

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In a preferred embodiment the method of producing 5-formyl-2-furylboronic acid comprises the steps of a) addition of lithium diisopropylamide to a composition comprising triisopropylborate and furfuraldiethylacetal and, optionally, a solvent, and b) acidic work-up of the reaction mixture of step a) and c) isolation of 5-formyl-2-furylboronic acid.

5-Formyl-2-furylboronic acid which is manufactured according to the teaching of the present invention is a white crystalline solid. The stability of the obtained 5-formyl-2-furylboronic acid is sufficient to employ said boronic acid as useful building-block to subsequent reactions in drug synthesis like the Suzuki coupling reaction. Furthermore, the reaction conditions and procedures are more convenient to a person skilled in the art and the reaction sequence is capable of providing a sufficient amount of 5-formyl-2-furylboronic acid.

The present invention is further illustrated by the following Examples without being limited thereto.

Example

A dried 500 mL 3-neck flask with mechanical stirrer, internal thermometer and addition funnel under nitrogen is charged with 20,16 g (0,118 mol) furfuraldiethylacetal, 33,4 g (0,177 mol) triisopropylborate and 40 mL of anhydrous THF. The water content of the reaction mixture was measured according to the Karl-Fischer-titration method and was determined to be less than 800 µg/mL of water. The solution is cooled to an internal temperature of -10°C. Keeping the temperature at -10°C to 0°C 84 mL (25 wt%, 1.84 M solution THF, heptane, ethylbenzene from Chemmetal, content determined by titration, 1.3 equivalents) LDA was added via addition funnel to the reaction mixture over a period of 1 hour. Using a canula the reaction mixture was subsequently transferred to precooled aqueous hydrochloric acid which was obtained by mixing 33 mL of concentrated

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hydrochloric acid and 55 mL water. The reaction temperature was maintained at a temperature of less than 30°C. The resulting tan slurry of 5-formyl-2-furylboronic acid was cooled to 0°C and filtered. The filter cake was washed
5 twice with 20 mL of cold water to give 17.6 g of wet cake. Drying (40°C, vacuum oven) gave 12.41 g of an off-white product. The overall yield of 5-formyl-2-furylboronic acid was 75%. The content of unreacted furfural in the crude product was determined to be less than 0.1%.

10 Optional Recrystallization:

A 2L neck flask with mechanical stirrer is charged with 130 g 5-formyl-2-furylboronic acid, 900 mL acetonitrile and 400 mL water. the resulting slurry is heated to reflux, at
15 which point the solids were in solution. The dark solution is cooled overnight to 0°C. The resulting slurry is filtered and washed with 100 mL of acetonitrile. Drying gives 116.7 g of 5-formyl-2-furylboronic acid as a white crystalline solid (90% yield).

5-Formyl-2-furylboronic acid synthesized according to the
20 method of the present invention is either with or without optional recrystallization stable at room temperature for more than one year. By way of contrast, 5-formyl-2-furylboronic acid synthesized according to methods known in the prior art decomposes spontaneously upon standing at
25 room temperature within days or hours.

Claims

1. A method of producing 5-formyl-2-furylboronic acid comprising the steps of:
 - a) addition of a base to a composition comprising a boric acid ester and 2-furaldehyde whereby the formyl functionality of the 2-furaldehyde is protected with a protective group, and
 - b) acidic work-up of the reaction mixture of step a), and
 - c) isolation of 5-formyl-2-furylboronic acid.
2. A method according to claim 1, characterized in that the boric acid ester of step a) is an alkyl boric acid ester and/or aryl boric acid ester.
3. A method according to claim 2, characterized in that the alkyl boric acid ester of step a) is selected from the group consisting of $B(O^iPr)_3$, $B(OEt)_3$, $B(OMe)_3$, $B(OPr)_3$, $B(Obu)_3$, and mixtures thereof.
4. A method according to claim 1, characterized in that the protective group of step a) is a O,O-acetal protective group or N,O-acetal protective group.
5. A method according to claim 4, characterized in that the acetal protective group of step a) is selected from the group consisting of alkanols having 1 to 10 carbon atoms, alkandiols having 1 to 20 carbon atoms, and mixtures thereof.
6. A method according to claim 1, characterized in that the base of step a) is selected from the group consisting of alkyl metal, metal amides, and mixtures thereof.
7. A method according to claim 6, characterized in that the base of step a) is selected from the group consisting of lithium hexamethyldisilazane, sodium hexamethyldisilazane, potassium hexamethyldisilazane,

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lithium diisopropylamide, butyl lithium, methyl lithium, ethyl lithium, propyl lithium, and mixtures thereof.

8. A method according to any of the preceding claims,
5 characterized in that a solvent is present in step a).
9. A method according to claim 8, characterized in that the solvent is selected from the group consisting of tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, and mixtures thereof.
- 10 10. A method according to claim 1, characterized in that the acidic work-up in step b) is conducted by using an aqueous acid.
11. A method according to claim 10, characterized in that the acid is selected from the group consisting of
15 hydrochloric acid, sulfuric acid, citric acid, acetic acid, formic acid, and mixtures thereof.
12. A method according to claim 10, characterized in that the isolation of 5-formyl-furan-boronic acid of step c) is carried out by means of filtration, centrifugation
20 and/or crystallization.
13. A method according to any of the preceding claims, characterized in that subsequent to step c) 5-formyl-furan-boronic acid is further purified by means of recrystallization.
- 25 14. A method according to any of the preceding claims comprising the steps of:
- a) addition of lithium diisopropylamide to a composition comprising triisopropylborate and furfuraldiethylacetal, and optionally a solvent, and
30 b) acidic work-up of the reaction mixture of step a), and
c) isolation of 5-formyl-2-furylboronic acid.

Abstract

The present invention refers to an improved method of producing 5-formyl-2-furylboronic acid. The method is carried out in a three-step process comprising the steps
5 of:

- a) addition of a base to a composition comprising a boric acid ester and 2-furaldehyde whereby the formyl functionality of the 2-furaldehyde is protected with a protective group, and
- 10 b) acidic work-up of the reaction mixture of step a), and
- c) isolation of 5-formyl-2-furylboronic acid.